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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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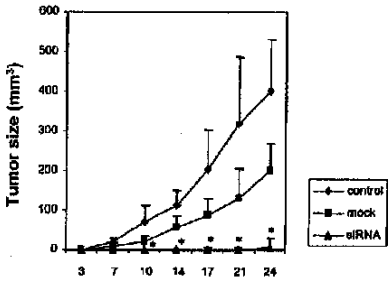
13 April 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: *c-met* siRNA ADENOVIRUS VECTORS INHIBIT CANCER CELL GROWTH, INVASION AND TUMORIGENICITY



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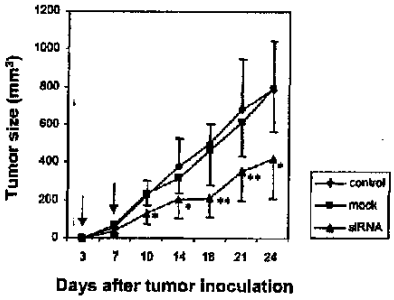

B

(57) Abstract: Suppression of the Hepatocyte growth factor/scatter factor (HGF/SF)-Met signaling pathway by targeting the Met protein tyrosine kinase was tested as strategy for suppressing tumor growth. Using RNA interference (RNAi) technology and adenoviruses carrying siRNA (Ad Met siRNA) target sequences dramatically reduced Met expression in mouse, dog and human tumor cells. Met was suppressed using Ad Met siRNA in mouse mammary tumor (DA3) cells and Met-transformed (NIH3T3 (M114) cells as well as human prostate cancer, sarcoma, glioblastoma, gastric and ovarian cancer cells. Furthermore, the Ad Met siRNA infection reversed transformed cell morphology. Ad Met siRNA killed cancer cells by inducing apoptosis. RNAi targeting Met suppressed HGF/SF-mediated scattering as well as ligand-mediated invasion activity and growth of tumor cells. Met siRNA infection also abrogated downstream Met signaling to molecules such as Akt and p44/42 MAPK. Importantly, the Met siRNA triggered apoptosis was correlated to suppressed tumorigenicity in vivo. Intro-tumoral infection with c-met siRNA adenovirus vectors produced significant reduction in tumor growth. Thus Met RNAi is an effective weapon for targeting Met expression and for treating c-Met$^+$ cancers.

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tional Application No
/US2005/010441

A. CLASSIFICATION OF SUBJECT MATTER
C12N15/11 C12N15/86

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/007754 A (RIGEL PHARMACEUTICALS, INC; HITOSHI, YASUMICHI; JENKINS, YONCHU; MARKO) 22 January 2004 (2004-01-22) paragraphs '0003!, '0005!, '0022!, '0272!; figure 6; example 4	1-47
X	WO 2004/020583 A (BRISTOL-MYERS SQUIBB COMPANY; HUANG, FEI; HAN, XIA; REEVES, KAREN, A;) 11 March 2004 (2004-03-11) page 10, line 11 - line 21 page 97 - page 98	1-47

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 January 2006	31/01/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Surdej, P

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tional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ABOUNADER R ET AL: "In vivo targeting of SF/HGF and c-met expression via U1snRNA/ribozymes inhibits glioma growth and angiogenesis and promotes apoptosis" FASEB JOURNAL (FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY), BETHESDA, US, vol. 16, no. 1, January 2002 (2002-01), pages 108-110, XP002249673 ISSN: 0892-6638 abstract page 109; figures 1,2	1-47
A	MA P C ET AL: "c-Met: Structure, functions and potential for therapeutic inhibition" CANCER AND METASTASIS REVIEWS, KLUWER ACADEMIC PUBLISHERS, DORDRECHT, NL, vol. 22, no. 4, December 2003 (2003-12), pages 309-325, XP002328700 ISSN: 0167-7659 the whole document	1-47
P,X	SHINOMIYA NARIYOSHI ET AL: "RNA interference reveals that ligand-independent met activity is required for tumor cell signaling and survival" CANCER RESEARCH, vol. 64, no. 21, 1 November 2004 (2004-11-01), pages 7962-7970, XP002361319 ISSN: 0008-5472 the whole document	1-47

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-3, 8-47 (all partially), 4-6 (all completely)

The specific sequences of claims 1-7 have, according to PCT Rule 13ter.1.d, not been searched since the sequence listing as present in the description does not comply with WIPO Standard ST 25 prescribed in the administrative instructions under Rule 5.2. The sequence listing has been furnished neither in paper form nor in machine readable form as provided for in the same instructions and the applicant has not remedied the disclosed deficiencies within the limit fixed in the invitation pursuant to Rule 13ter.1.a. The search is therefore limited to RNAi having sequence complementary to mRNA encoded by human c-met, murine c-met, or c-met of another mammalian source, so that expression of said RNAi molecule in a cell that normally expresses c-met results in diminution or loss of expression of said mRNA. For the search, c-met is understood from the description as Met proto-oncogene tyrosine kinase, receptor of scatter factor/hepatocyte growth factor.

Although claims 21-38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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ernational application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-3, 8-47 (all partially), 4-6 (all completely)
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ıation on patent family members

ᵃᵗonal Application No
JS2005/010441

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004007754 A	22-01-2004	AU 2003249284 A1	02-02-2004
		EP 1576173 A2	21-09-2005
WO 2004020583 A	11-03-2004	AU 2003278725 A1	19-03-2004
		EP 1572957 A2	14-09-2005